PATENT
Customer Number 22,852
Attorney Docket No. 6483.0009-07

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Keith E. Langley *et al.*

Serial No.: 08/397,320

Filed: March 2, 1995

For: METALLOPROTEINASE INHIBITOR

Group Art Unit: 1648

Examiner: L. Scheiner

RECEIVED
MAR 2 2 2001
TECH CENTER 1600/2900

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF KEITH E. LANGLEY

I, Keith E. Langley, do hereby make the following declaration:

1. I am a co-inventor of U.S. Application Serial No. 08/397,320 ("the '320 application"), which claims priority based on U.S. Application No. 07/355,027 filed May 19, 1989 ("the '027 application"). I am employed by Amgen Inc., which is the assignee of the '320 application. My position is Senior Medical Writer II.

2. In 1988 and 1989, I worked for Amgen Inc. and my position was Research Scientist II.

3. Example 5 of the '320 application describes a method for purifying recombinant human TIMP-2 from *Escherichia coli* using three column chromatography steps: anion exchange chromatography on DEAE Sepharose® Fast Flow, cation exchange chromatography on CM Sepharose® Fast Flow, and gel filtration on Sephacryl® S-200 HR. On page 45, lines 1-4, it is stated: "A sample of the human MI

[TIMP-2] preparation described (about 6.5 µg) was subjected to amino-terminal amino acid sequencing through 18 cycles, using the method described in Example 2."

4. To the best of my knowledge, I have never submitted a sample of human TIMP-2 purified by the method described in Example 5 for amino acid sequencing.

5. On February 3, 1989, I did, however, submit a sample of human TIMP-2 prepared by a substantially similar procedure for amino acid sequencing. That sample was purified using two chromatography columns: anion exchange chromatography on Q Sepharose® and cation exchange chromatography on Mono S®. The results of the amino acid sequence analysis of that sample were reported to me by Patricia Fausset and Hsieng Lu in a memorandum dated March 13, 1989, which is appended hereto as Exhibit A. To my knowledge, this is the only sample of recombinant human TIMP-2 purified from *E. coli* at Amgen Inc. that was sequenced prior to the filing date of the '027 application. I would not have submitted a second sample of recombinant TIMP-2 from *E. coli* for amino-terminal sequence analysis simply because the purification procedure was modified as described in Example 5.

6. Based on the above, I believe that the '320 application mistakenly suggests on page 47, lines 5-8, that the amino-terminal sequence of recombinant human TIMP-2 was determined using a sample purified as described in Example 5 of that application. In fact, I believe that the TIMP-2 protein sample that was sequenced was the sample submitted by me on February 3, 1989, which was purified using a two step chromatography process, not the three step process described in Example 5.

7. The N-terminal amino acid sequencing data discussed in Example 5 are not needed to provide support for a claim directed to human TIMP-2 having the

sequence in Figure 2 of the application. If one expresses a protein in *E. coli* according to Example 4 and purifies that protein according to Example 5, one will obtain protein having the sequence in Figure 2, regardless of whether the N-terminal amino acid sequence is confirmed. The amino acid sequence data simply confirm the protein sequence predicted from the human TIMP-2 DNA clone in Figure 2 of the application, which was used to express the protein. The choice between two methods by which the recombinant protein was purified from *E. coli* has no bearing on whether the correct amino acid sequence was expressed from that clone.

8. Moreover, whether the '320 application indicates that amino acid sequencing was performed on a sample of human TIMP-2 prepared in *E. coli* using a two chromatography column protocol or whether that application incorrectly indicates that the sample sequenced was prepared by the similar three chromatography column protocol in Example 5 is not an important distinction to one skilled in the art.

9. The mistake regarding the identity of the protein sample sequenced was made without intent on my part to deceive the United States Patent and Trademark Office.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: February 27, 2001 By: Keith E. Langley
Keith E. Langley

PATENT
Customer Number 22,852
Attorney Docket No. 6483.0009-07

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Keith E. Langley *et al.*

Serial No.: 08/397,320

Filed: March 2, 1995

For: METALLOPROTEINASE INHIBITOR

Group Art Unit: 1648

Examiner: L. Scheiner

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF THOMAS C. BOONE

I, Thomas C. Boone, do hereby make the following declaration:

1. I am a co-inventor of U.S. Application Serial No. 08/397,320 ("the '320 application"), which claims priority based on U.S. Application No. 07/355,027 ("the '027 application") filed May 19, 1989. I am employed by Amgen Inc., which is the assignee of the '954 application. My position is Director of Process Science.

2. In 1988 and 1989, I worked for Amgen Inc. and my position was Research Scientist II.

3. Example 5 of the '320 application describes a method for purifying recombinant human TIMP-2 from *Escherichia coli* using three column chromatography steps: anion exchange chromatography on DEAE Sepharose® Fast Flow, cation exchange chromatography on CM Sepharose® Fast Flow, and gel filtration on Sephacryl® S-200 HR. On page 45, lines 1-4, it is stated: "A sample of the human MI

[TIMP-2] preparation described (about 6.5 µg) was subjected to amino-terminal amino acid sequencing through 18 cycles, using the method described in Example 2."

4. To the best of my knowledge, I have never submitted a sample of human TIMP-2 purified by the method described in Example 5 for amino acid sequencing. That method was, however, the best mode known to me for purifying TIMP-2 from *E. coli* at the time the '027 application was filed.

5. I am aware that one of my co-inventors, Dr. Keith Langley, submitted a sample of human TIMP-2 prepared by a substantially similar procedure for amino acid sequencing. It is my understanding that the sample submitted by Dr. Langley was purified using two chromatography columns: anion exchange chromatography on Q Sepharose® and cation exchange chromatography on Mono S®. The results of the amino acid sequence analysis of that sample were reported to me by Patricia Fausset and Hsieng Lu in a memorandum dated March 13, 1989, which is appended hereto as Exhibit A. To my knowledge, this is the only sample of recombinant human TIMP-2 purified from *E. coli* at Amgen Inc. that was sequenced prior to the filing date of the '027 application. I would not have submitted a second sample of recombinant TIMP-2 from *E. coli* for amino-terminal sequence analysis simply because the purification procedure was modified as described in Example 5.

6. Based on the above, I believe that the '320 application mistakenly suggests on page 45, lines 1-4, that the amino-terminal sequence of recombinant human TIMP-2 was determined using a sample purified as described in Example 5 of that application. In fact, I believe that the TIMP-2 protein sample that was sequenced was the sample submitted by Dr. Langley, which was purified using a two step

chromatography process, not the three step process described in Example 5.

7. The N-terminal amino acid sequencing data discussed in Example 5 are not needed to provide support for a claim directed to human TIMP-2 having the sequence in Figure 2 of the application. If one expresses a protein in *E. coli* according to Example 4 and purifies that protein according to Example 5, one will obtain protein having the sequence in Figure 2, regardless of whether the N-terminal amino acid sequence is confirmed. The amino acid sequence data simply confirm the protein sequence predicted from the human TIMP-2 DNA clone in Figure 2 of the application, which was used to express the protein. The choice between two methods by which the recombinant protein was purified from *E. coli* has no bearing on whether the correct amino acid sequence was expressed from that clone.

8. Moreover, whether the '320 application indicates that amino acid sequencing was performed on a sample of human TIMP-2 prepared in *E. coli* using a two chromatography column protocol or whether that application incorrectly indicates that the sample sequenced was prepared by the similar three chromatography column protocol in Example 5 is not an important distinction to one skilled in the art.

9. The mistake regarding the identity of the protein sample sequenced was made without intent on my part to deceive the United States Patent and Trademark Office.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under

Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 2/27/2001 By: Thomas C. Boone
Thomas C. Boone

PATENT
Customer Number 22,852
Attorney Docket No. 6483.0009-07

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Keith E. Langley *et al.*

Serial No.: 08/397,320

Filed: March 2, 1995

For: METALLOPROTEINASE INHIBITOR

Group Art Unit: 1648

Examiner: L. Scheiner

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

DECLARATION OF YVES A. DE CLERCK

I, Yves A. De Clerck, do hereby make the following declaration:

1. I am a co-inventor of U.S. Application Serial No. 08/397,320 ("the '320 application"), which claims priority based on U.S. Application No. 07/355,027 filed May 19, 1989. I am employed by Childrens Hospital Los Angeles., which is an assignee of the '954 application. My position is Vice-President of Research and Professor of Pediatrics, Biochemistry and Molecular Biology.

2. In 1988 and 1989, I worked for Childrens Hospital Los Angeles.

3. Example 5 of the '320 application describes a method for purifying recombinant human TIMP-2 from *Escherichia coli* and states: "A sample of the human MI [TIMP-2] preparation described (about 6.5 µg) was subjected to amino-terminal amino acid sequencing through 18 cycles, using the method described in Example 2."

4. The work on expressing recombinant human TIMP-2 in *E. coli* and on purifying that protein from *E. coli* was performed at Amgen Inc, not in my laboratory at Childrens Hospital Los Angeles.

5. I had no knowledge at the time and I do not know now what sample of recombinant human TIMP-2 was submitted for N-terminal amino acid sequencing or how that sample was purified.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: March 1, 2001

By: _____
Yves A. De Clerck